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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/782,570	02/19/2004	Nadine Carozzi	045600/274144	5780

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EXAMINER	
KUBELIK, ANNE R	

ART UNIT	PAPER NUMBER
1638	

DATE MAILED: 11/30/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Advisory Action Before the Filing of an Appeal Brief	**Application No.** 10/782,570	**Applicant(s)** CAROZZI ET AL.	
	Examiner Anne R. Kubelik	**Art Unit** 1638	

--The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

THE REPLY FILED 18 October 2006 FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE.

1. ☐ The reply was filed after a final rejection, but prior to or on the same day as filing a Notice of Appeal. To avoid abandonment of this application, applicant must timely file one of the following replies: (1) an amendment, affidavit, or other evidence, which places the application in condition for allowance; (2) a Notice of Appeal (with appeal fee) in compliance with 37 CFR 41.31; or (3) a Request for Continued Examination (RCE) in compliance with 37 CFR 1.114. The reply must be filed within one of the following time periods:
   a) ☐ The period for reply expires _____months from the mailing date of the final rejection.
   b) ☐ The period for reply expires on: (1) the mailing date of this Advisory Action, or (2) the date set forth in the final rejection, whichever is later. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of the final rejection.

   Examiner Note: If box 1 is checked, check either box (a) or (b). ONLY CHECK BOX (b) WHEN THE FIRST REPLY WAS FILED WITHIN TWO MONTHS OF THE FINAL REJECTION. See MPEP 706.07(f).

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

NOTICE OF APPEAL

2. ☒ The Notice of Appeal was filed on *18 October 2006*. A brief in compliance with 37 CFR 41.37 must be filed within two months of the date of filing the Notice of Appeal (37 CFR 41.37(a)), or any extension thereof (37 CFR 41.37(e)), to avoid dismissal of the appeal. Since a Notice of Appeal has been filed, any reply must be filed within the time period set forth in 37 CFR 41.37(a).

AMENDMENTS

3. ☐ The proposed amendment(s) filed after a final rejection, but prior to the date of filing a brief, will not be entered because
   (a) ☐ They raise new issues that would require further consideration and/or search (see NOTE below);
   (b) ☐ They raise the issue of new matter (see NOTE below);
   (c) ☐ They are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or
   (d) ☐ They present additional claims without canceling a corresponding number of finally rejected claims.

   NOTE: _____. (See 37 CFR 1.116 and 41.33(a)).
4. ☐ The amendments are not in compliance with 37 CFR 1.121. See attached Notice of Non-Compliant Amendment (PTOL-324).
5. ☒ Applicant's reply has overcome the following rejection(s): 112, 2nd.
6. ☐ Newly proposed or amended claim(s) _____ would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s).
7. ☒ For purposes of appeal, the proposed amendment(s): a) ☐ will not be entered, or b) ☒ will be entered and an explanation of how the new or amended claims would be rejected is provided below or appended.
   The status of the claim(s) is (or will be) as follows:
   Claim(s) allowed: _____.
   Claim(s) objected to: _____.
   Claim(s) rejected: *1-11, 19 and 22-23*.
   Claim(s) withdrawn from consideration: _____.

AFFIDAVIT OR OTHER EVIDENCE

8. ☒ The affidavit or other evidence filed after a final action, but before or on the date of filing a Notice of Appeal will not be entered because applicant failed to provide a showing of good and sufficient reasons why the affidavit or other evidence is necessary and was not earlier presented. See 37 CFR 1.116(e).
9. ☐ The affidavit or other evidence filed after the date of filing a Notice of Appeal, but prior to the date of filing a brief, will not be entered because the affidavit or other evidence failed to overcome all rejections under appeal and/or appellant fails to provide a showing a good and sufficient reasons why it is necessary and was not earlier presented. See 37 CFR 41.33(d)(1).
10. ☐ The affidavit or other evidence is entered. An explanation of the status of the claims after entry is below or attached.

REQUEST FOR RECONSIDERATION/OTHER

11. ☒ The request for reconsideration has been considered but does NOT place the application in condition for allowance because: See Continuation Sheet.
12. ☐ Note the attached Information Disclosure Statement(s). (PTO/SB/08) Paper No(s). _____
13. ☐ Other: _____.

Continuation of 11. does NOT place the application in condition for allowance because:

112, 1st, enablement:

Applicant urges that the Office appears to requiring that every pesticidal protein encompassed by the claims could be used successfully without experimentation. This is not found persuasive; the only requirement is that the claimed nucleic acids can be made without undue experimentation; for the reasons of record, they are not.

Applicant urges that the conclusion that the claimed nucleic acids are not enablement seems to be based solely on the number of possible nucleic acids, without consideration of the other wands factors, the guidance in the specification, and the working examples. This is not found persuasive because the working examples and the general guidance in the specification do not overcome the unpredictability associated with the very large number of possible nucleic acids.

Applicant urges that guidance is provided in the specification and the art. This is not found persuasive for the reasons of record.

Applicant urges that all that is needed is to make variants and test them using routine methods. This is not found persuasive for the reasons of record.

Applicant urges that Genetech supports their assertion that the specification is enabled because in that case the specification provided no guidance on how to make hGH using cleavable fusion expression, whereas here the specification provides guidance in the form of specific nucleic acid sequences and guidance in making variants. This is not found persuasive because the guidance is making variants is not specific enough to make up to 111 amino acid substitutions in the protein, as encompassed by the instant claims.

Applicant urges that the specification need not disclose what is well-known in the art. This is not found persuasive because SEQ ID NO:1-4 are not known in the art and the proteins appears to be very different to what is known in the art. AXMI-007 has the most similarity to cry proteins with toxicity only to mosquito (cry4Aa, cry10Aa and cry19Ba) but its toxicity to the Euhemipteran L. lineolaris suggests that AXMI-007 is a new class of cry toxin.

Applicant urges that the specification teaches conserved residues that are not likely to tolerate substitution. This is not found persuasive because "one of skill in the art would understand that functional variants may have minor conserved or nonconserved alterations in the conserved residues" (pg 13, lines 7-8). Thus, it does not teach that conserved residues that are not likely to tolerate substitution.

Applicant urges that there is no claim equivalent to Amgen's all EPO analogs. This is not found persuasive. From Amgen, pg 1026: "The district court found that over 3,600 different EPO analogs can be made by substituting at only a single amino acid position, and over a million different analogs can be made by substituting three amino acids. The patent indicates that it embraces means for preparation of 'numerous' polypeptide analogs of EPO. Thus, the number of claimed DNA encoding sequences that can produce an EPO-like product is potentially enormous." The number of possible variants (19^{744} or 4^{2235}, which can also be stated as 2.5×10^{951} or 4.0×10^{1345}, respectively) in the instant case is much, much greater that those found to not be enabled in Amgen.

Applicant urges that Lazar and Hill altered conserved amino acids, which one of skill in the art would expect would lead to loss of function. This is not found persuasive because the instant specification teaches that conserved amino acids can be substituted, and "one of skill in the art would understand that functional variants may have minor conserved or nonconserved alterations in the conserved residues" (pg 13, lines 7-8). Lazar and Hill point to the fallacy of this teaching as a generality, indicating that more specific guidance must be provided.

Applicant urges that the majority of conserved substitutions in nonconserved regions have little or no effect on protein function. This is not found persuasive because the specification, on pg 13, lines 1-8, suggest making conserved substitutions based on conserved regions, which Lazar and Hill teach is not predictable.

Applicant makes arguments based on exhibits that will not be considered because Applicant did not provide a showing of good and sufficient reasons of why they were necessary and not earlier presented. Thus, no response can be made by the examiner.

Applicant urges that the codon table can be used to determine modifications that would not affect biological activity of the encoded protein, and the specification teaches conserved amino acids. These are not found persuasive. The codon table can be used to make substitutions that do not change the proteins sequences; these were already stated to be enabled. Making amino acid substitutions, to the extent encompassed by the claims, is not.

Applicant repeats arguments previously made about Guo et al. These are not found persuasive for the reasons of record.

Applicant urges that making amino acids with 95% identity to SEQ ID NO:2 or 4 does not require random substitutions. This is not found persuasive; a protein with 95% identity to SEQ ID NO:2 has 37 amino acid substitutions relative to it. As no guidance is provided as to which 37 amino acids are to be substituted, random substitutions must be done.

Applicant repeats arguments previously made about Li et al. These are not found persuasive for the reasons of record.

Applicant makes more arguments based on exhibits that will not be considered because Applicant did not provide a showing of good and sufficient reasons of why they were necessary and not earlier presented. Thus, no response can be made by the examiner.

Applicant urges that while they do not presume that every conceivable conservative substitution in a non conserved region will produce a function la protein, experimentation required to make them is not undue. This is not found persuasive because the claims encompass nucleic acids encoding proteins with up to 111 amino acid substitutions, yet the specification does not teach a single such nucleic acid. The references cited in the Office action teach that substitutions of even a few amino acids is unpredictable and that unpredictability increases as the numbers of substitutions are increased. Thus, the experimentation required would be undue.

Applicant urges that that a case was not made that the claims are not enabled. This is not found persuasive for the reasons of record.

The portion of the rejection with respect to complementary sequences is withdrawn.

112, 1st, written description:

Applicant urges that all that is needed is a disclosed correlation between function and structure, and the instant claims are drawn to nucleic acids encoding proteins with 95% identity to SEQ ID NO:2 or 4 or to nucleic acids with 95% identity to SEQ ID NO: 1 or 3. This is not found persuasive because the structural feature responsible for the claimed function is not described. As even a single amino acid substitution in a cry protein may alter its insecticidal specificity (Tounsi et al, 2003, J. Appl. Microbiol. 95:23-28; see pg 27, column

2, paragraph 2). The only pesticidal activity described in the specification is against L. lineolaris the structural features required for this activity are not described.

Applicant repeats arguments previously made about Li et al. These are not found persuasive for the reasons of record.

Applicant repeats arguments previously made about structure and function. These are not found persuasive for the reasons of record.

Applicant urges that that a case was not made that the claimed nucleic acids are not described. This is not found persuasive for the reasons of record.

ANNE KUBELIK, PH.D.
PRIMARY EXAMINER